



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/JP96/03722 <b>(22) International Filing Date:</b> 20 December 1996 (20.12.96)  <b>(30) Priority Data:</b> 7/354654                      22 December 1995 (22.12.95)                      JP  <b>(71) Applicants (for all designated States except US):</b> KOWA COMPANY, LTD. [JP/JP]; 6-29, Nishiki 3-chome, Naka-ku, Nagoya-shi, Aichi-ken 460 (JP). NISSAN CHEMICAL INDUSTRIES, LTD. [JP/JP]; 7-1, Kanda-Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 101 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MURAMATSU, Toyojiro [JP/JP]; 2-13-14, Nakata, Shizuoka-shi, Shizuoka 422 (JP). MASHITA, Katsumi [JP/JP]; 473-12, Kawajiri, Fuji-shi, Shizuoka 417 (JP). SHINODA, Yasuo [JP/JP]; 74-1, Babacho, Shizuoka-shi, Shizuoka 420 (JP). SASSA, Hironori [JP/JP]; M1-A, Highgrace, 620-22, Hara, Numazu-shi, Shizuoka 420 (JP). KAWASHIMA, Hiroyuki [JP/JP]; A-3, Kowa-Fujiso, 3-5-6, Imai, Fuji-shi, Shizuoka 417 (JP). TANIZAWA, Yoshio [JP/JP]; 230-1, Takamatsubarakosai, Okayama-shi, Okayama 701-13 (JP). TAKEUCHI, Hideatsu [JP/JP]; 332-1, Aza-Nakanotori, Oaza-Onoshinden, Fuji-shi, Shizuoka 417 (JP).		<b>(74) Agents:</b> SAEKI, Norio et al.; 2nd Tsuchiya Building, 9th floor, 30-9, Taito 1-chome, Taito-ku, Tokyo 110 (JP).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION STABILIZED WITH A BASIC AGENT  <b>(57) Abstract</b> <p>Disclosed is a pharmaceutical composition comprising (E)-3,5-dihydroxy-7-[4'-4''-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester, of which the aqueous solution or dispersion has a pH of from 7 to 8. The composition has good time-dependent stability and has no change in its outward appearance even after having been stored long.</p>		

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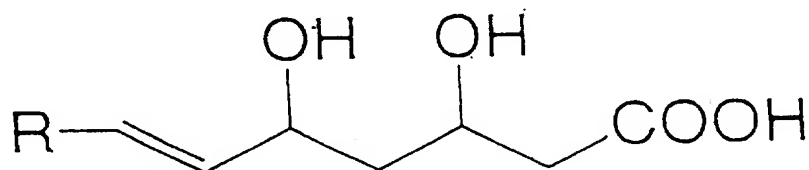
## PHARMACEUTICAL COMPOSITION STABILIZED WITH A BASIC AGENT

## TECHNICAL FIELD

The present invention relates to a pharmaceutical composition with high stability and, more precisely, to a pharmaceutical composition comprising an HMG-CoA reductase inhibitor of which the stability varies depending on its pH, especially (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester.

## BACKGROUND ART

It is known that 7-substituted-3,5-dihydroxy-6-heptenoic acids of a general formula:

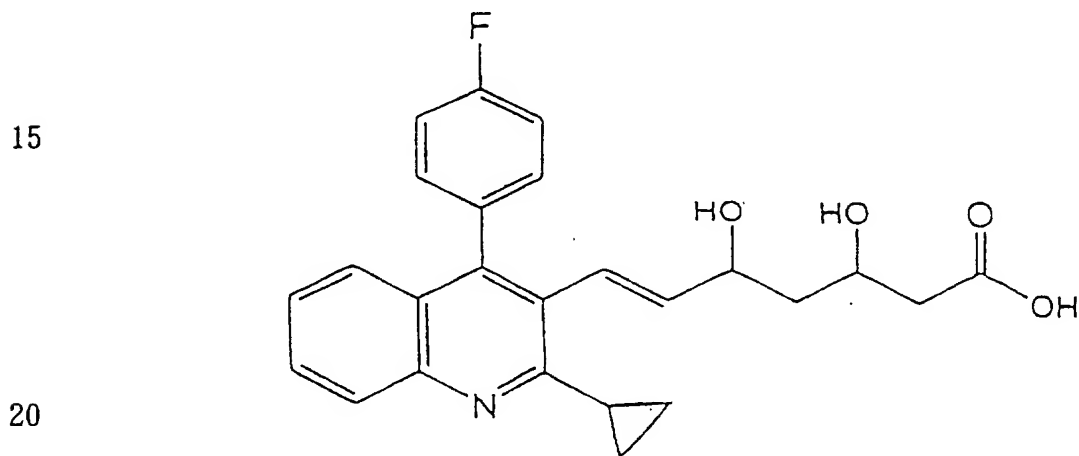


wherein R represents an organic group, have HMG-CoA reductase-inhibiting activity, and are useful as medicines for hyperlipemia and also as medicines for atherosclerosis (see U.S. Patent 4,739,073, U.S. Patent 5,001,255, U.S. Patent 4,751,235, U.S. Patent 4,804,679, Japanese Patent Application Laid-Open No. 1-279866).

However, these 7-substituted-3,5-dihydroxy-6-heptenoic acids are unstable at low pH, and require some particular means for formulating them into preparations. A means of

formulating them along with an alkaline medium, such as calcium carbonate or sodium carbonate, into preparations with pH of 8 or higher (see Japanese Patent Application Laid-Open No. 5-246844), and a means of formulating them along with a  
5 basic agent, such as magnesium oxide or sodium hydroxide, into preparations with pH of 9 or higher (see Japanese Patent Application Laid-Open No. 2-6406) have been proposed.

(E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid (hereinafter this may be referred to as NK-104) to be represented by a structural  
10 formula:



or its salt or ester is one of HMG-CoA reductase inhibitors that are represented by the above-mentioned general formula, and is known to be useful as a medicine for hyperlipemia and  
25 also as a medicine for atherosclerosis (see Japanese Patent Application Laid-Open No. 1-279866). NK-104 is also unstable at low pH, and many difficulties have been encountered in formulating it into preparations.

It has been reported that these HMG-CoA reductase inhibitors are formulated into preparations with pH 8 or higher, desirably pH 9 or higher, but unexpectedly, it has been found that NK-104 and its salts and esters are still  
5 unstable even within a high pH range.

Therefore, preparations comprising NH-104 or its salt or ester, if formulated in conventional manners, have low time-dependent stability, and are problematic in that their  
10 outward appearance changes with the lapse of time. Given the situation, the development of stable preparations comprising it is desired.

#### SUMMARY OF THE INVENTION

15 We, the present inventors have variously studied in order to obtain stable pharmaceutical compositions comprising NK-104 and, as a result, have found unexpectedly that NK-104 is stable within a relatively low pH range. On the basis of this finding, we have completed the present invention.

20

In addition, we have further found that, if a basic substance is added to a pharmaceutical composition comprising NK-104 in such a manner that the aqueous solution or dispersion of the composition may have pH of from 7 to 8, the  
25 composition is stable.

An object of the present invention is to provide a pharmaceutical composition comprising NK-104, or its salt or ester, of which the aqueous solution or dispersion has pH of

from 7 to 8, preferably has pH of from 7.0 to 7.8, more preferably has pH of from 7.1 to 7.8.

5 The present invention also provides a medicinal preparation comprising NK-104, or its salt or ester, of which the aqueous solution or dispersion has pH of from 7 to 8, preferably has pH of from 7.0 to 7.8, more preferably has pH of from 7.1 to 7.8.

10 The present invention further provides a pharmaceutical composition comprising an HMG-CoA reductase inhibitor, of which the aqueous solution or dispersion has pH of from 7 to 8, preferably has pH of from 7.0 to 7.8, more preferably has pH of from 7.1 to 7.8.

15 The active ingredient of the composition of the present invention is NK-104 to be represented by the above-mentioned structural formula. The configuration in this substance, NK-104 is not specifically defined herein. In addition, NK-104 may be in any form of its salts and esters. The salts include, for example, sodium salt, potassium salt and calcium salt. Preferred is calcium salt of NK-104.

#### DETAILED DESCRIPTION OF THE INVENTION

25 The pH as referred to herein indicates the pH value to be determined in such a manner that a unit dose of a solid preparation comprising NK-104 or its salt or ester is sampled and dissolved or dispersed in from 1 to 10 ml of pure water, and the pH of the resulting aqueous solution or dispersion is

measured.

A basic substance may be added to the pharmaceutical composition comprising NH-104 to control the pH of the composition, which may be any of antacids and pH regulators including, for example, antacids such as magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium aluminate, dry aluminium hydroxide, synthetic hydrotalcite, synthetic aluminium silicate, magnesium carbonate, precipitated calcium carbonate, magnesium oxide, aluminium hydroxide, and sodium hydrogencarbonate; and pH regulators such as L-arginine, sodium phosphate, disodium hydrogenphosphate, sodium dihydrogenphosphate, potassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate, disodium citrate, sodium succinate, ammonium chloride, and sodium benzoate. Of these, preferred are magnesium metasilicate aluminate, L-arginine, and dipotassium hydrogenphosphate.

The pharmaceutical composition of the present invention can be formulated into various forms of preparations, but preferred are peroral solid preparations. For example, the composition may be formulated into tablets, granules, powders, troches, capsules, chewables, film-coated preparations of these, and even sugar-coated preparations thereof.

Where the pharmaceutical composition of the present invention is formulated into such peroral solid preparations,

any of vehicles (excipients), binders, disintegrators and lubricants can be added thereto, if desired. The preparations may be formulated from the composition along with any of these, in any ordinary manner.

5

The vehicles (excipients) include, for example, lactose, corn starch, denatured corn starch, mannitol, sorbitol, wood cellulose, fine crystalline cellulose and calcium carbonate, which can be used either singly or as  
10 combined.

The binders include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, and partial saponificates of  
15 these, which can be used either singly or as combined. Especially preferred is hydroxypropylmethyl cellulose.

The disintegrators include, for example, hydroxypropyl cellulose with a low degree of substitution, carmellose, sodium carboxystarch, calcium carmellose, corn starch, partially-alpha-ized starch, sodium closcarmellose and  
20 clospovidone, which can be used either singly or as combined. Especially preferred is Low substituted hydroxypropyl cellulose.

25

The lubricants includes, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate and talc, which can be used either singly or as combined.



The amounts of the ingredients constituting the composition of the present invention are not specifically defined. For example, the amount of NK-104 or its salt or ester may be from 0.01 to 40 % by weight, preferably from 0.05 to 10 % by weight, more preferably from 0.5 to 5 % by weight; and the basic substance may be added to the composition in such an amount that is necessary for making the aqueous solution or dispersion of the composition have pH of from 7 to 8. Where the composition is formulated into peroral solid preparations, it is desirable that the vehicle is added thereto in an amount of from 30 to 95 % by weight, the binder in an amount of from 1 to 20 % by weight, the disintegrator in an amount of from 1 to 30 % by weight, and the lubricant in an amount of from 0.5 to 10 % by weight.

15

If further desired, any additional components, such as sweeteners, flavorings and colorants may also be added to the composition of the present invention.

20

The necessary amount of the basic substance to be added to the composition of the invention in order to make the aqueous solution or dispersion of the composition have pH of from 7 to 8 may be from about 1 to 6.5 % by weight or so, if magnesium metasilicate aluminate is used singly, or from about 0.1 to 1.7 % by weight or so, if dipotassium hydrogenphosphate is used singly, of from about 0.01 to 0.1 % by weight or so, if L-arginine is used singly, or from about 0.1 to 2 % by weight or so, if sodium hydrogencarbonate is used singly. As mentioned above, it is preferable that the basic substance is

used singly. However, two or more such basic substances can be used in combination.

The composition of the present invention can be coated  
5 to give film-coated tablets or sugar-coated tablets. As the coating base, for example, usable are celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose; and also aminoalkyl methacrylate copolymer E, white sugar, and pullulan. As the plasticizer for the base, for example,  
10 usable are macrogol 6000, triethyl citrate, and triacetylpropylene glycol.

The pharmaceutical composition of the present invention can be produced according to any ordinary methods  
15 employable in producing peroral solid preparations. If stirring granulation is employed, this may be conducted as follows. First, NK-104, a basic substance, a vehicle, a binder and a disintegrator are mixed. Next, water is added to the resulting mixture, then granulated with stirring, dried  
20 and dressed to give dry granules. Further, the granules are mixed with a lubricant, and pelletized with a pelletizer into pellets. Also employable is fluidized bed granulation, which may be conducted as follows. First, NK-104, a basic substance, a vehicle and a disintegrator are mixed. Then, an  
25 aqueous solution of a binder is sprayed over the resulting mixture, using a fluidized bed granulator, to prepare granules. These granules are mixed with a lubricant, and then pelletized with a pelletizer into pellets.

Using ordinary coating devices, the pellets as produced according to the above-mentioned methods can be coated with a solution or suspension comprising a coating base and optionally a plasticizer and a colorant to give film-coated tablets or sugar-coated tablets.

#### BEST MODES OF CARRYING OUT THE INVENTION

Examples of the pharmaceutical composition of the present invention are mentioned below, which, however, are not intended to restrict the scope of the invention. In the following examples, the low substituted hydroxypropyl cellulose was commercially available as sold for a medicine additive and contains from 5-16% of  $\text{OC}_3\text{H}_6\text{OH}$  group. Hydroxypropylmethyl cellulose 2910 contains 28-30%  $\text{OCH}_3$  and 7-12%  $\text{OC}_3\text{H}_6\text{OH}$ . Both low substituted hydroxypropyl cellulose and hydroxypropylmethyl cellulose 2910 as used in the examples are described in The Pharmacopoeia of Japan, 12th edition.

#### Example 1:

Herein produced were tablets each having the composition mentioned below.

	Calcium Salt of NK-104	1.0 mg
	Lactose	101.4
	Low Substituted Hydroxypropyl Celulose	12.0
25	Hydroxypropylmethyl Cellulose 2910	2.0
	Magnesium Metasilicate Aluminate	2.4
	<u>Magnesium Stearate</u>	<u>1.2</u>
	Total (one tablet)	120.0

The components of the above-mentioned composition, except magnesium stearate, were mixed to prepare a homogeneous powdery mixture, to which was added a suitable amount of pure  
5 water. The resulting mixture was granulated with stirring, and pelletized to give pellets. Magnesium stearate was added to and mixed with these pellets, which were then tabletted into NK-104-containing tablets

10 Example 2:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below.

	Calcium Salt of NK-104	1.0 mg
	Lactose	102.8
15	Low Substituted Hydroxypropyl Cellulose	12.0
	Hydroxypropylmethyl Cellulose 2910	2.0
	Dipotassium Hydrogenphosphate	1.0
	<u>Magnesium Stearate</u>	<u>1.2</u>
20	Total (one tablet)	120.0

Example 3:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below.

25	Calcium Salt of NK-104	1.0 mg
	Lactose	103.7
	Low Substituted Hydroxypropyl Cellulose	12.0
	Hydroxypropylmethyl Cellulose 2910	2.0
	L-arginine	0.1

<u>Magnesium Stearate</u>	<u>1.2</u>
Total (one tablet)	120.0

## Example 4:

5           In the same manner as in Example 1, herein produced  
were tablets each having the composition mentioned below.

	Calcium Salt of NK-104	1.0 mg
	Lactose	103.2
	Low Substituted Hydroxypropyl Cellulose	12.0
10	Hydroxypropylmethyl Cellulose 2910	2.0
	Magnesium Metasilicate Aluminate	0.6
	<u>Magnesium Stearate</u>	<u>1.2</u>
	Total (one tablet)	120.0

## 15   Test 1:

The pH of a 5 % suspension of tablets produced in any  
of Examples 1 to 4 (the suspension was prepared by suspending  
one tablet in 2.4 ml of pure water) was measured.

20           After having been stored at 60°C for 2 weeks, the  
percentage retention of calcium salt of NK-104 in the tablets  
was measured according to HPLC. After having been stored at  
60°C for 3 days, the change in the outward appearance of the  
tablets was observed. The test results are shown in Table 1.

25

Table 1

	Example 1	Example 2	Example 3	Example 4
pH of 5% Suspension	7.8	7.7	7.5	7.1
Percentage Retention of Ca NK-104	97 %	97 %	93 %	92 %
Change in Outward Appearance	No change	No change	No change	No change

Control Examples 1 to 3:

In the same manner as in Example 1, herein produced were control tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5 % suspension of each tablet, the percentage retention of Ca NK-104, and the change in the outward appearance of the tablets. The test results are shown in Table 2.

Table 2

		Control Example 1	Control Example 2	Control Example 3
5	Ca NK-104	1.0 mg	1.0 mg	1.0 mg
	Lactose	103.8	98.8	98.8
	Hydroxypropyl Cellulose with Low Degree of Substitution	12.0	12.0	12.0
	Hydroxypropylmethyl Cellulose 2910	2.0	2.0	2.0
10	Sodium Ascorbate		5.0	
	Ascorbic Acid			5.0
	Magnesium Stearate	1.2		
	Total (one tablet)	120.0	120.0	120.0
	pH of 5 % Suspension	6.6	6.3	3.3
15	Percentage Retention of Ca NK- 104, after stored at 60°C for 2 weeks	88 %	77 %	38 %
	Change in Outward Appearance, after stored at 60°C for 3 days	No change	No change	No change

As in Tables 1 and 2 showing the test results, it is obvious that the percentage retention of Ca NK-104 in the 5 % suspension of the composition having pH of 7 or higher is high, after having been stored at 60°C for 2 weeks, while the same in the 5 % suspension thereof having pH of lower than 7 becomes lower with the decrease in the pH value thereof.

Example 5, and Control Example 4:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5 % suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 3.

15



Table 3

	Example 5	Control Example 4
Ca NK-104	1.0 mg	1.0 mg
Lactose	101.4	93.9
Hydroxypropyl Cellulose with Low Degree of Substitution	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
Magnesium Metasilicate Aluminate	2.4	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5 % Suspension	7.8	8.3
Change in Outward Appearance, after stored at 60°C for 3 days	No change	Changed to pale yellowish brown

Example 6, and Control Example 5:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5 % suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 4.

Table 4

	Example 6	Control Example 5
Ca NK-104	1.0 mg	1.0 mg
Lactose	103.7	93.9
Hydroxypropyl Cellulose with Low Degree of Substitution	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
L-arginine	0.1	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5 % Suspension	7.5	9.8
Change in Outward Appearance, after stored at 60°C for 3 days	No change	Changed to pale yellowish green

Example 7, and Control Example 6:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5 % suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 5.

Table 5

5		Example 7	Control Example 6
	Ca NK-104	1.0 mg	1.0 mg
	Lactose	101.8	93.9
	Hydroxypropyl Cellulose with Low Degree of Substitution	12.0	12.0
10	Hydroxypropylmethyl Cellulose 2910	2.0	2.0
	Sodium Hydrogencarbonate	2.0	9.9
	Magnesium Stearate	1.2	1.2
	Total (one tablet)	120.0	120.0
	pH of 5 % Suspension	7.8	9.8
15	Change in Outward Appearance, after stored at 60°C for 3 days	No change	Changed to dark navy blue

20 Example 8, and Control Example 7:

In the same manner as in Example 1, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5 % suspension of each tablet, and the  
25 change in the outward appearance of the tablets. The test results are shown in Table 6.

Table 6

	Example 8	Control Example 7
Ca NK-104	1.0 mg	1.0 mg
Lactose	102.8	93.9
Hydroxypropyl Cellulose with Low Degree of Substitution	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
Dipotassium Hydrogenphosphate	1.0	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5 % Suspension	7.7	8.4
Change in Outward Appearance, after stored at 60°C for 3 days	No change	Changed to orange

As is obvious from the test results in Tables 3 to 6, no change in the outward appearance of the tablets was found when the 5 % suspensions of the tablets had pH of 8 or lower, even after having been stored at 60°C for 3 days, but the outward appearance of the tablets changed when the 5 % suspensions of the tablets had pH of higher than 8.

## INDUSTRIAL APPLICABILITY OF THE INVENTION

The pharmaceutical composition of the present invention has good time-dependent stability, with having no change in  
5 the outward appearance thereof even after having been stored long. Therefore, the composition is good in medical use, especially in the form of peroral solid preparations.

The pharmaceutical composition of the present invention  
10 that contains NK-104 or salt or ester thereof are especially useful for treating a patient, particularly a human, that is suffering from or susceptible to hyperlipemia or atherosclerosis by administering the pharmaceutical composition to such patient.

15

Particularly preferred unit dosage have been described in the examples above. It will be appreciated the specifically preferred dosage amounts of a pharmaceutical composition of the invention used in a given therapy will vary according to  
20 various known factors such as the particular compositions formulated, the specific compound utilized, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in  
25 the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

The invention has been described in detail with reference to preferred embodiments thereof. However, it will be

appreciated that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements within the spirit and scope of the invention as set forth in the following claims.

5

## C L A I M S

1. A pharmaceutical composition comprising (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester, of which the aqueous solution or dispersion has pH of from 7 to 8.

2. A pharmaceutical composition comprising (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester, to which is added a basic substance to make the aqueous solution or dispersion of the composition have pH of from 7 to 8.

3. The pharmaceutical composition as claimed in claim 1 or 2, wherein the salt of (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid is potassium salt of the acid.

4. The pharmaceutical composition as claimed in claim 2 or 3, wherein the basic substance is one or more selected from antacids and pH regulators.

5. The pharmaceutical composition as claimed in claim 4, wherein the antacid is potassium metasilicate aluminate.

6. The pharmaceutical composition as claimed in claim 4, wherein the pH regulator is L-arginine or dipotassium hydrogenphosphate.

7. The pharmaceutical composition as claimed in any one of claims 1 to 6, which further contains at least one of vehicles, disintegrators, binders and lubricants.

8. The pharmaceutical composition as claimed in any one of claims 1 to 7, which is a peroral solid preparation.

9. The pharmaceutical composition as claimed in claim 7 or 8, wherein the vehicle is lactose.

10. The pharmaceutical composition as claimed in any one of claims 7 to 9, wherein the disintegrator is hydroxypropyl cellulose with a low degree of substitution.

11. The pharmaceutical composition as claimed in any one of claims 7 to 10, wherein the binder is hydroxypropylmethyl cellulose.



# INTERNATIONAL SEARCH REPORT

International Application No  
PC./JP 96/03722

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K9/20 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 356 896 A (KABADI MOHAN B ET AL) 18 October 1994 cited in the application see page 13; example 13 see column 2, line 51 - column 3, line 5 ---	1,2,4,7, 8
A	EP 0 304 063 A (NISSAN CHEMICAL IND LTD) 22 February 1989 cited in the application see page 41; example 1 ---	1
A	EP 0 520 406 A (NISSAN CHEMICAL IND LTD) 30 December 1992 see page 10, line 29; figure 4 --- -/--	3

☒ Further documents are listed in the continuation of box C.

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International Application No

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